Hormone Replacement Therapy: Fact versus Fiction Part 2

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Basics of Menopause

- Definition: Permanent cessation of menstruation occurring after loss of ovarian activity
- Determination of this occurs 1 year after last menstrual period
- In North America, median age of menopause is 51, with 95% of women becoming menopausal between age 45 to 55
- Many women may undergo physiologic changes associated with menopause in years proceeding the final menstrual period
  - This interval is often referred to as perimenopause—more recently—menopausal transition
The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women

<table>
<thead>
<tr>
<th>Stage</th>
<th>-5</th>
<th>-4</th>
<th>-3b</th>
<th>-3a</th>
<th>-2</th>
<th>-1</th>
<th>+1a</th>
<th>+1b</th>
<th>+1c</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td><strong>REPRODUCTIVE</strong></td>
<td><strong>MENOPAUSAL TRANSITION</strong></td>
<td><strong>POSTMENOPAUSE</strong></td>
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<tr>
<td>Menstrual cycle</td>
<td>Variable to regular</td>
<td>Regular</td>
<td>Regular</td>
<td>Subtle changes in flow/length</td>
<td>Variable length: Persistent ≥7-day difference in length of consecutive cycles</td>
<td>Interval of amenorrhea of &gt;60 days</td>
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</tr>
<tr>
<td>Duration</td>
<td>Variable</td>
<td>1-3 years</td>
<td>2 years (1+1)</td>
<td>3-6 years</td>
<td>Remaining lifespan</td>
<td></td>
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**PRINCIPAL CRITERIA**

- Menstrual cycle
- Variable to regular
- Regular
- Regular
- Subtle changes in flow/length
- Variable length: Persistent ≥7-day difference in length of consecutive cycles
- Interval of amenorrhea of >60 days

**SUPPORTIVE CRITERIA**

- **Endocrine**
  - **FSH**
  - Low
  - Low
  - Variable*
  - Variable*
  - Variable*
  - Variable*
  - >25 IU/L*
  - Low
  - Low
  - Low
  - Low
  - Low
  - Very low
  - Very low

- **AMH**
  - Low
  - Low
  - Low
  - Low
  - Very low
  - Very low

- **Inhibin B**
  - Low
  - Low
  - Low
  - Low
  - Very low
  - Very low

**DESCRIPTIVE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Reproductive symptoms</th>
<th>Vasomotor symptoms</th>
<th>Vasomotor symptoms</th>
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<tbody>
<tr>
<td></td>
<td>Likely</td>
<td>Likely</td>
<td>Likely</td>
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<tr>
<td></td>
<td>Increasing symptoms of urogenital atrophy</td>
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Arrow: elevated; FMP: final menstrual period; FSH: follicle-stimulating hormone; AMH: anti-müllerian hormone.
* Blood draw on cycle days 2 to 5.
• Approximate expected level based on assays using current international pituitary standard.

Menopause transition is marked by fluctuation in hormone levels
- Estradiol and progesterone decrease
- FSH increases
Vasomotor (hot flushes) and vaginal symptoms most closely associated with hormonal changes
These signs and symptoms can be alleviated with use of Hormone Replacement Therapy or Menopausal hormone therapy (MHT) — broad term used to describe:
- Unopposed estrogen (ET) — in those with history of hysterectomy
- Combined estrogen-progestin (EPT) — in those with intact uterus to prevent estrogen-associated endometrial hyperplasia/cancer
Signs/Symptoms

- Vasomotor symptoms: sudden sensation of extreme heat in upper body → hot flush
  - Typically last 1-5 mins
  - Can also have perspiration, flushing, chills, clamminess and anxiety
- Overall duration of hot flushes unclear, but reports show median duration of 4 yrs and 10 yrs

- Vaginal Atrophy: direct consequence of hypoestrogenic state in menopause resulting in anatomic & physiologic changes in genitourinary tract
- Symptoms may include: vaginal or vulvar dryness, discharge, itching and dyspareunia
Menopausal Hormone Therapy (MHT)

- Goal of therapy is to relieve menopausal symptoms, most importantly hot flushes (vasomotor symptoms).
- Other associated symptoms of menopause that could respond to therapy as well are:
  - Mood lability/depression
  - Vaginal atrophy
  - Sleep disturbances (when related to hot flashes)
- Systemic hormone therapy, either estrogen alone (ET) or in combination with progestin (EPT) is most effective therapy for vasomotor symptoms related to menopause.
• Indications/Candidates for MHT:
  o ET or EPT reasonable option for most women in late 40s or 50s with moderate to severe vasomotor symptoms
  o Exception: those with history of breast cancer, CHD, previous VTE or stroke, acute liver disease or those at high risk for these complications
• What about age of patient?
  o WHI study demonstrated adverse effects of MHT in older postmenopausal women (over age 60)
  o Most often this is not the group seeking therapy for symptoms→mainly in late 40s or 50s
  o Those in this age group should be reassured that absolute risk of complications for those whom are young and taking MHT for five years is low

• MHT not recommended to treat depression or for prevention of issues with cognitive function or dementia
• No longer recommended for prevention of chronic disease
  o CHD: use of MHT not recommended even in young postmenopausal women
  o Osteoporosis: previously estrogen recommended as first-line choice for prevention and treatment, however now Bisphosphonates recommended as first choice
  • On occasion if patient with persistent menopausal symptoms who can not tolerate first or second line treatments for osteoporosis, estrogen may be reasonable option
MHT cont...

- All routes of administration appear equally effective for symptom relief (& bone density)
- Routes of ET: orally or transdermally in the forms of patches, gels or sprays
- Routes of Progestins: oral (most commonly used)
- Some studies show risk of VTE and stroke appear to be higher with oral versus transdermal therapy
- All women with intact uterus need progestin to prevent endometrial hyperplasia/cancer associated with use of unopposed estrogen
- Those without uterus, should not receive progestin → NO other health benefits other than prevention of endometrial hyperplasia/cancer
• Common side effects: breast tenderness, vaginal bleeding, bloating, headaches and mood symptoms

• Duration: Treat with lowest effective dose for shortest duration needed to relieve vasomotor symptoms
  o 2-3 years, generally no more than 5 years

• Discontuation: may be associated with recurrent vasomotor symptoms in 50% of women
  o Insufficient evidence to recommend whether abrupt or tapering method is best to prevent recurrent symptoms
### Hormonal options for vasomotor symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage/Regimen</th>
<th>FDA approved</th>
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<tbody>
<tr>
<td>ET or EPT (standard dose)</td>
<td>Conjugated ET 0.625 mg/dMicronized estradiol 1 mg/dTransdermal estradiol 0.0375-0.05 mg/d</td>
<td>Y</td>
</tr>
<tr>
<td>Estrogen combined w/estrogen agonist/antagonist</td>
<td>**Conjugated estrogen 0.45 mg/d and Bazedoxifene 20 mg/d</td>
<td>Y</td>
</tr>
<tr>
<td>Progestin</td>
<td>Medroxyprogesterone 2.5 mg/d</td>
<td>N</td>
</tr>
<tr>
<td>*Compounded bioidentical hormones</td>
<td></td>
<td>N</td>
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**As an alternative to progestin use, FDA recently approved a combined daily oral preparation of conjugated estrogen and bazedoxifene (Duavee) -used for treatment of vasomotor symptoms and to prevent osteoporosis in postmenopausal women with intact uterus**
• Compounded Biodentical Hormones
  o Plant derived hormones chemically similar or structurally identical to those produced in the body
  o Include products approved by FDA → micronized progesterone & estradiol
  o Compounded preparations are not approved by FDA
  o Because of lack of FDA oversight, most compounded preparations have not undergone clinical testing for safety and efficacy
  o There is concern for purity, potency and quality of compounded preparations
  o Under and over dosage possible because of variable bioavailability and bioactivity
  o Given available data and lacking evidence to support superiority claims of compounded bioidentical hormones over conventional MHT → conventional MHT is recommended and preferred
Nonhormonal options for vasomotor symptoms

<table>
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<tr>
<th>Treatment</th>
<th>Dosage/Regimen</th>
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<tr>
<td>SSRIs and SSNRIss</td>
<td></td>
<td>N</td>
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<tr>
<td>Paroxetine</td>
<td>7.5 mg/d</td>
<td>Y</td>
</tr>
<tr>
<td>Venlaxafine</td>
<td>37.5 mg/d</td>
<td>N</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1mg/d</td>
<td>N</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>600-900 mg/d</td>
<td>N</td>
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<tr>
<td>Phytoestrogens</td>
<td></td>
<td>N</td>
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<tr>
<td>Herbal remedies</td>
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</table>
• Selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), clonidine and gabapentin are effective alternatives to MHT for treatment of vasomotor symptoms.

• Although data mixed, results from RCTs support effectiveness of SSRIs and SSNRIs for treatment of vasomotor symptoms in healthy, non-depressed women.

• Reported adverse effects: nausea, dizziness, dry mouth, nervousness, constipation, sexual dysfunction generally resolve with time or dose adjustment.
• Paroxetine (Brisdelle) ➔ 7.5 mg/day only non-hormonal therapy FDA approved for treatment of vasomotor symptoms

• Clonidine ➔ 0.1 mg/day; antihypertensive
  o Has been used to treat vasomotor symptoms; not FDA approved for treatment of vasomotor symptoms
  o Common adverse effects: dry mouth, insomnia, drowsiness

• Venlaxafine ➔ 37.5 mg/d; SSNRI
  o Not FDA approved for treatment of vasomotor symptoms

• Gabapentin ➔ 600-900 mg/day; anticonvulsant
  o Shown to reduce vasomotor symptoms in several studies, but not FDA approved for this indication
  o RCT using 900 mg/day showed 45% reduction in hot flush frequency and 54% reduction in severity
  o Common adverse effects: dizziness, somnolence and peripheral edema
• Natural Products: several natural products used for management of vasomotor symptoms—in U.S. none of these therapies are regulated by FDA and not tested for safety, efficacy or purity

• Data does not show Phytoestrogens (soybeans, soy products, red clover), herbal supplements (black cohosh, ginseng, St. John’s wort & ginkgo biloba) and lifestyle modifications are efficacious for treatment of vasomotor symptoms
# Hormonal options for vaginal atrophy

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<th>Treatment</th>
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| **Estrogen $\rightarrow$ systemic:** Standard dose | Conjugated ET 0.625 mg/d  
Micronized estradiol 1 mg/d  
Transdermal 0.0375-0.05 mg/d | Y            |
| ET $\rightarrow$ Vaginal/Local | Estradiol ring 7.5 mcg/d                                       | Y            |
|                                | Estradiol Vaginal tab 10 mcg/d                                  | Y            |
|                                | Estradiol ring 0.05 mg/d                                       | Y            |
|                                | Estradiol cream 2 g/d                                          | Y            |
|                                | Conjugated estrogen cream 0.5-2.0 g/d                          | Y            |
• Estrogen therapy effectively alleviates symptoms

• Local therapy is recommended in patients with only vaginal symptoms

• Systemic absorption of vaginal estrogen has been documented in those using daily dose of 25 micrograms of estradiol
  o Theoretic concern that systemic absorption may increase risk of endometrial cancer

• Cochrane meta-analysis of 19 trials found local estrogen not associated with increased risk of endometrial cancer, therefore progestin for endometrial protection is not needed
Non-hormonal options for vaginal atrophy

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<th>Treatment</th>
<th>Dosage/regimen</th>
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<tbody>
<tr>
<td>Raloxifene &amp; Tamoxifen</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>*Ospemifene (Osphena)</td>
<td>60 mg/d</td>
<td>Y</td>
</tr>
<tr>
<td>Vaginal lubricants</td>
<td></td>
<td>N</td>
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<tr>
<td>Vaginal moisturizers</td>
<td></td>
<td>N</td>
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*studies suggest Ospemifene improves vaginal atrophy without stimulating endometrium
-usually given as 60 mg/d oral tablet
-common adverse effects: hot flushes, vaginal discharge, muscle spasms and excessive sweating
-FDA approved for the treatment of moderate-severe dyspareunia in postmenopausal women
• Vaginal lubricants
  o Water based or silicone based lubricants and moisturizers may alleviate vaginal symptoms related to menopause
  o Limited data regarding effectiveness
  o Prospective studies have demonstrated vaginal moisturizers improve dryness, pH balance and elasticity and reduce vaginal itching, irritation and dyspareunia
Risks of MHT

- Risks: ET & EPT→thromboembolic disease and breast cancer
  - Majority of trials including WHI used preparations containing conjugated equine estrogens alone or with medroxyprogesterone acetate
  - Use of alternative forms of estrogen and progestin may be associated with different risk profile
  - Observation studies suggest transdermal estrogen may lower risk of VTE compared with oral regimens
  - RCTs needed to compare safety and efficacy of different regimens
In October 2013, published in JAMA, was a follow up study of WHI with 13 yrs of cumulative follow-up data. Findings:

- Overall risks of EPT during intervention phase outweighed benefits
- Most of these risks dissipated post intervention, however:
  - Cardiovascular events remained elevated
  - Reduction in endometrial cancer
  - Hip fractures remained reduced
  - Breast cancer remained high
- For those on ET (hx of hysterectomy), risks and benefits during intervention phase more balanced
  - Increased risk of stroke and VTE
  - Reduced hip fractures
  - Non-significant reduction in breast cancer

• For both cancer and cardiovascular disease, the EPT arm had more adverse outcomes than ET only.

• The findings also suggest MHT has harmful effect on CHD risk among older women.

• The current WHI findings based on the intervention phase, postintervention phase and current cumulative follow-up phase, do not support use of EPT or ET for chronic disease prevention.

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial; JAMA. 2002;288(3):321-333.
From: Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women’s Health Initiative Randomized Trials

Women with hx of Breast CA

• Vasomotor symptoms: lifestyle modifications, alternative and complimentary therapy and pharmacologic agents
  o Variety of low-dose antidepressants or Gabapentin can be used
  o Use of hormonal therapy generally contraindicated in those with breast cancer

• Vaginal atrophy: treatment options have been limited because of little data on safety and efficacy of traditional topical therapies in those with breast cancer
  o Many studies demonstrated success of local hormone therapy for vaginal dryness, but variable rates of estrogen absorption raises safety concern for patients with breast cancer
• There is no randomized controlled data assessing safety of these topical treatments in those with breast cancer

• Therefore given lack of data, non-hormonal methods should be considered first-line treatment for vaginal atrophy in women with history of hormone sensitive breast cancer
How about women over 65?

- Many women will continue to have vasomotor symptoms after age 65
- Decision to continue MHT should be individualized and be based on woman’s symptoms and risk-benefit ratio regardless of age
- Because some women aged 65 and older may need to continue systemic hormone therapy for management of vasomotor symptoms, American Congress of Obstetricians and Gynecologists (ACOG) and North American Menopause Society (NAMS) recommends against routine discontinuation of systemic hormone therapy at age 65
Summary of Recommendations

• Menopausal hormone therapy (ET or EPT) is currently indicated for management of vasomotor symptoms or vaginal atrophy
• Formulations include oral, transdermal or vaginal
• Progestins should be used in all women with intact uteri using systemic MHT to prevent endometrial hyperplasia or cancer
• Women without uteri, progestin should not be used as there is no other health benefit
• Long term use for prevention of chronic diseases is no longer recommended
• Duration ➞ lowest effective dose for 2-3 yrs and generally no more than 5 years
• For discontinuation, based on WHI, 55% women will have recurrent symptoms if abruptly stopped, therefore can taper, however not proven to be more effective
• Risks associated with MHT: CHD, stroke, VTE and breast CA
• Benefits: decreased hip fracture and colorectal cancer
• Adverse outcomes related to age and tend to occur more often in older women
• In women with history of breast cancer, MHT for treatment of vasomotor symptoms is contraindicated
• Non-hormonal methods should be considered first-line treatment for vaginal atrophy in those with history of breast cancer
• ACOG and NAMS recommend against routine discontinuation of MHT in those over age 65 secondary to many needing treatment for management of continued vasomotor symptoms
References

• ACOG committee opinion #532. Compounded Bioidentical Menopausal Hormone Therapy. August 2012 (Reaffirmed 2014)
• Barbieri, Robert L and Martin, Kathryn A. Treatment of menopausal symptoms with hormone therapy. August 2015. UpToDate.